

### **REMARKS/ARGUMENTS**

A Final Office Action was issued October 25, 2007. Applicant filed an Amendment December 26, 2007 responsive to the Final Office Action. However, the Amendment was not entered and an Advisory Action was subsequently issued January 8, 2008. Accordingly, Applicant hereby submits the Preliminary Amendment, concurrently with an RCE request.

#### **Status of the Claims:**

Claims 1-81 were pending in the present application. Of them, claims 1-24 and 75-81 were examined and claims 25-74 were withdrawn as directed to non-elected subject matter. By this Preliminary Amendment, claims 1-3, 5, 7, 12-14, 16-19, 23, 75, 77, 78, 80, and 81 are amended and claims 8, 9, 21, and 22 are canceled.

#### **The October 25, 2007 Office Action:**

In the October 25, 2007 Final Office Action, the Examiner rejected claims 1-4, 6, 8-15, 17, 19, 21-24, 75, 76, and 78-80 under 35 U.S.C. §103(a) as being unpatentable over U.S. Pub. US2003/0107386 to Dodgson et al. (hereinafter "Dodgson"). Claims 5, 7, 16, 18, and 20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson, in view of U.S. Patent No. 6,482,619 to Rubinsky et al. (hereinafter "Rubinsky"). Claims 77 and 81 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson, in view of U.S. Pat. Pub. US 2002/018627 to Wang et al. (hereinafter "Wang").

In the January 8, 2008 Advisory Action, claims 1-24 and 75-81 remained rejected.

Applicant appreciates the Examiner's careful review of the application.

In response, as set forth above, claims 1-3, 5, 7, 12-14, 16-19, 23, 75, 77, 78, 80, and 81 have been amended and claims 8, 9, 21, and 22 have been canceled.

Support for the amendments can be found in the disclosure as originally filed, and particularly page 62, lines 25-32 to page 66, lines 1-22 of the specification and Figs. 5A, 5B, and 5C of the drawings as originally filed. Applicant submits that no new matter has been added.

Any amendments to the claims not specifically referred to herein as being included for the purpose of distinguishing the claims from cited references are included for the purpose of clarification, consistence and/or grammatical/spelling correction only.

It is now believed that the application is in condition for allowance and such allowance is respectfully requested.

The following remarks herein are considered to be responsive thereto.

***35 U.S.C. §103(a) Rejections***

In the October 25, 2007 Office Action, claims 1-4, 6, 8-15, 17, 19, 21-24, 75, 76, and 78-80 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson. Applicant respectfully traverses the rejections at least for the reasons set forth below.

**Claim 1:**

As set forth above, amended claim 1 recites a device for monitoring status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, that requires:

- a. "a first substrate having a first surface and an opposite second surface;
- b. *a second substrate supported by the first substrate*, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein the body portion defines a first passage between the first side surface, and the second side surface, and a first opening on the first surface of the second substrate that is in fluid communication with the first passage;
- c. sidewalls positioned above the first surface of the second substrate;
- d. *a third substrate positioned over the sidewalls and the second substrate* and having a first surface and an opposite second surface, wherein the third substrate, the sidewalls and the second substrate define a chamber, and wherein the chamber is in fluid communication with a second passage defined by portions of the sidewalls and the third substrate;
- e. at least one sensor positioned in the first passage proximate to the first opening, *wherein the cell is positioned in the chamber and the intracellular space of the cell is in fluid communication with the first passage through the first opening of the second substrate;*

- f. at least one seal element positioned on the second substrate and proximate to the first opening, for sealing the cell to the second substrate in operation;
- g. *a pair of first controls positioned inside the first passage, between the first surface of the first substrate and the second surface of the second substrate, for controlling the flow of a medium through the first passage; and*
- h. *a second control positioned inside the second passage, for controlling the flow of a medium through the second passage.”* (Emphasis added.)

In the present application as originally filed, and in particular, page 62, lines 25-32 to page 66, lines 1-22 of the specification and Figs. 5A, 5B, and 5C of the drawings, several exemplary embodiments are disclosed of a device for monitoring status of at least one cell, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein.

In one embodiment, as shown in Figs. 5A, 5B, and 5C, the device 500 has a first substrate 550 with a first surface 551 and an opposite second surface 553, *a second substrate 560 supported by the first substrate 550* having a first surface 561, an opposite second surface 563, a body portion 502 between the first surface 561 and the second surface 563, a first side surface 565, and an opposite second side surface 567. As shown, the body portion 502 defines a first passage 511 between the first side surface 565, and the second side surface 567, and first openings 569 on the first surface 561 of the second substrate that are in fluid communication with the first passage 511. Sidewalls 571, 573, 575 are positioned over the first surface 561 of the second substrate. *A third substrate 580 is positioned over the sidewalls 571, 573, 575 and the second substrate 560*, with a first surface 581 and an opposite second surface 583. The sidewalls 571, 573, 575, partition the space between the second substrate 560 and the third substrate 580 into chambers 590, 592, above the first surface 561 of the second substrate such that only one of the first openings 569 distributed on and over the first surface 561 of the second substrate is located between the sidewalls of a corresponding chamber 590, 592. Each chamber 590, 592 is in fluid communication with at least one neighboring chamber through a second passage 593 defined over a corresponding sidewall 571, 573, 575 and under the second surface of the third substrate 583. Sensors 505 are positioned in the first passage 511 proximate to a corresponding one of the first openings 569. Each cell 501 is positioned in a corresponding

chamber 590,592 and *the intracellular space 543 of each cell 501 is in fluid communication with the first passage 511 through the first openings 569*. Seal elements 503 are positioned on the second substrate 560 and proximate to a corresponding first opening 569, for sealing each cell 501 to the second substrate 560 in operation. *First controls 509A, 509B, 509C are positioned inside the first passage 511, for controlling the flow of a medium through the first passage 511. Second controls 521A, 521B, and 521C are positioned inside the second passage 593, for controlling the flow of a medium through the second passage 593.*

In contrast, as understood by applicant, Dodgson discloses an apparatus for making measurements on objects in a medium, which has *an orifice* formed in a surface adapted such that *the object seals the orifice* to create first and second cavity portions. (Dodgson, [0001]-[0003]).

Dodgson does not teach or suggest a device having “a first substrate..., [and] *a second substrate supported by the first substrate...*,” as disclosed in amended claim 1 of the present invention.

Moreover, Dodgson does not teach or suggest a device having these limitations and also having “*a third substrate positioned over the sidewalls and the second substrate ...*” as disclosed in amended claim 1 of the present invention. In the October 25, 2007 Office Action, the Examiner concedes that Dodgson *does not teach* “an embodiment in which a third substrate and sidewalls are both formed above the second substrate to define a reaction chamber and a second passage.”

Still further, Dodgson does not teach or suggest a device having all of the above-mentioned limitations of amended claim 1, and also having “at least one sensor ..., *wherein the cell is positioned in the chamber and the intracellular space of the cell is in fluid communication with the first passage through the first opening,*” as disclosed in amended claim 1 of the present invention. As set forth above, Dodgson discloses an apparatus for making measurements on objects in a medium, which has *an orifice* formed in a surface adapted such that *the object seals the orifice*. (Dodgson, [0001]-[0003]). As shown in Figs. 1-8 of Dodgson, the object 30 is intentionally lodged in the orifice 16 such that *no fluid communication* exists between the intracellular space of the object 30 and channel 14, which teaches away from the instant invention of amended claim 1.

Furthermore, Dodgson does not teach or suggest a device with all of the above-mentioned limitations and also having *“a pair of first controls positioned inside the first passage, for controlling the flow of a medium through the first passage”* and/or *“a second control positioned inside the second passage, for controlling the flow of a medium through the second passage,”* as disclosed by amended claim 1 of the present invention.

Therefore, Dodgson does not teach or suggest a device having *“a first substrate...; a second substrate supported by the first substrate, ...a third substrate positioned over the sidewalls and the second substrate...; at least one sensor ..., wherein the cell is positioned in the chamber and the intracellular space of the cell is in fluid communication with the first passage through the first opening; at least one seal element...; a pair of first controls positioned inside the first passage, for controlling the flow of a medium through the first passage; and a second control positioned inside the second passage, for controlling the flow of a medium through the second passage,”* and having all of the other limitations required by amended claim 1 of the present invention.

For at least the foregoing reasons, independent claim 1, as amended, is patentable under 35 U.S.C. §103(a) over Dodgson.

Accordingly, claims 2-7, 10, 11, and 75-77, which depend from now allowable amended claim 1, are patentable for at least this reason.

Claims 2-7, 10, 11, and 75-77 also contain additional patentable subject matter. For example, claim 10 recites a device “wherein the first passage is in fluid communication with a reservoir of a medium,” and claim 11 recites a device “wherein the second passage is in fluid communication with a reservoir of a medium.” Dodgson does not teach or suggest a device for monitoring status of at least one cell wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, having either of these limitations, taken alone or in combination with the limitations recited in claim 1 of the present invention. The Examiner concedes in the October 25, 2007 Office Action that Dodgson *does not teach* “the use of reservoirs in communication with the first and second passages.” Accordingly, individual consideration of each claim is respectfully requested.

**Claim 12:**

As set forth above, amended claim 12 recites a device for monitoring status of a plurality of cells, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, that requires:

- a. "a first substrate having a first surface and an opposite second surface;
- b. ***a second substrate supported by the first substrate***, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein the body portion defines a first passage between the first side surface and the second side surface and a plurality of first openings distributed on and over the first surface of the second substrate, wherein each of the plurality of first openings is in fluid communication with the first passage;
- c. ***a third substrate positioned over the second substrate***, having a first surface and an opposite second surface, and spaced apart from the second substrate thereby defining a space between the second surface of the third substrate and the first surface of the second substrate;
- d. ***a plurality of sidewalls positioned between the second substrate and the third substrate thereby partitioning the space between the second substrate and the third substrate into a plurality of chambers above the first surface of the second substrate*** such that only one of the first openings distributed on and over the first surface of the second substrate is located between the sidewalls of a corresponding chamber, wherein each chamber is in fluid communication with at least one neighboring chamber through a second passage defined over the sidewalls and under the second surface of the third substrate;
- e. ***a plurality of sensors positioned in the first passage, each sensor being proximate to a corresponding one of the first openings distributed on and over the first surface of the second substrate***, wherein each cell is positioned in a corresponding one of the chambers and the intracellular space of each cell is in fluid communication with the first passage through the first opening located between the sidewalls of a corresponding chamber;

- f. *a plurality of seal elements positioned on the second substrate for sealing a corresponding cell to the second substrate in operation*, wherein each seal element is proximate to a corresponding one of the plurality of first openings;
- g. *a plurality of first controls positioned inside the first passage*, wherein each chamber has a pair of corresponding first controls for controlling flow of the medium through portions of the first passage that correspond to that chamber; and
- h. *a plurality of second controls, wherein each second control is positioned inside a corresponding second passage for controlling the flow of a medium through that second passage.*"  
(Emphasis added.)

Incorporating herein first the reasons set forth above why amended claim 1 is patentable, applicant respectfully submits that independent claim 12, as amended, is patentable under 35 U.S.C. §103(a) over Dodgson for at least this reason. Amended claim 12 is also patentable for the additional reasons set forth below.

In the present application as originally filed, and in particular, page 62, lines 25-32 to page 66, lines 1-22 of the specification and Figs. 5A, 5B, and 5C of the drawings, and as discussed above in connection with amended claim 1, several exemplary embodiments are disclosed of a device for monitoring status of a plurality of cells, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space.

In contrast, as understood by applicant, Dodgson discloses an apparatus for making measurements on objects in a medium, with *an orifice* formed in a surface adapted such that *the object seals the orifice*. An array of test positions may be formed on *a single substrate*. (Dodgson, [0001]-[0010]).

Dodgson does not teach or suggest a device having "a first substrate...; [and] *a second substrate supported by the first substrate*..." as disclosed in amended claim 12 of the present invention.

Moreover, Dodgson does not teach or suggest a device having the above-mentioned limitations and also having "*a third substrate positioned over the second substrate* ..." as disclosed in amended claim 12 of the present invention.

Still further, Dodgson does not teach or suggest a device having all the limitations mentioned above, and also having ***“a plurality of sidewalls positioned between the second substrate and the third substrate thereby partitioning the space between the second substrate and the third substrate into a plurality of chambers above the first surface of the second substrate*** such that only one of the first openings distributed on and over the first surface of the second substrate is located between the sidewalls of a corresponding chamber, wherein each chamber is in fluid communication with at least one neighboring chamber through a second passage defined over the sidewalls and under the second surface of the third substrate,” as disclosed in amended claim 12 of the present invention.

Furthermore, Dodgson does not teach or suggest a device having all the above-mentioned limitations and also having ***“a plurality of seal elements positioned on the second substrate for sealing a corresponding cell to the second substrate in operation, wherein each seal element is proximate to a corresponding one of the plurality of first openings,”*** as disclosed in amended claim 12 of the present invention.

Moreover, Dodgson does not teach or suggest a device having all the limitations mentioned above, and also having ***“a plurality of first controls positioned inside the first passage, wherein each chamber has a pair of corresponding first controls for controlling flow of the medium through portions of the first passage that correspond to that chamber;”*** and/or having ***“a plurality of second controls, wherein each second control is positioned inside a corresponding second passage for controlling the flow of a medium through that second passage,”*** as disclosed in amended claim 12 of the present invention.

Therefore, Dodgson does not teach or suggest a device as required by amended claim 12 of the present invention.

For at least the foregoing reasons, independent claim 12, as amended, is patentable under 35 U.S.C. §103(a) over Dodgson.

Accordingly, claims 13-20, 23, 24, and 78-81, which depend from now allowable amended claim 12, are patentable for at least this reason.

Claims 13-20, 23, 24, and 78-81 also contain additional patentable subject matter. For example, claim 23 recites a device “wherein at least one chamber is in fluid communication with a reservoir of a medium through a corresponding second passage” and claim 24 recites a device



“wherein the first passage is in fluid communication with a reservoir of a medium.” Dodgson does not teach or suggest a device for monitoring status of a plurality of cells, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, having either of these limitations, taken alone or in combination with the limitations recited in claim 12 of the present invention. The Examiner concedes in the October 25, 2007 Office Action that Dodgson *does not teach* “the use of reservoirs in communication with the first and second passages.” Accordingly, individual consideration of each claim is respectfully requested.

**Claims 8, 9, 21, and 22:**

As set forth above, by this amendment claims 8, 9, 21, and 21 are canceled. Accordingly, these rejections are considered moot.

**Claims 5, 7, 16, 18, and 20:**

In the October 25, 2007 Office Action, claims 5, 7, 16, 18, and 20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson, in view of Rubinsky.

As set forth above, claims 5 and 7 are dependent on now allowable amended claim 1, and claims 16, 18, and 20 are dependent on now allowable amended claim 12. Accordingly, these rejections are considered moot, and claims 5, 7, 16, 18, 20 are patentable under 35 U.S.C. §103(a) over Dodgson and Rubinsky, for at least this reason.

Claims 5, 7, 16, 18, and 20 also contain additional patentable subject matter. For example, amended claim 7 recites a device “wherein when a first medium is introduced into the first passage, a second medium is introduced into the chamber through the second passage, the intracellular space of the cell is in fluid communication with the first passage having the first medium, and at least part of the membrane of the cell is in contact with the second medium in the chamber, the sensor measures the responses of the cell to the first medium and the second medium,” and claim 18 recites a device “wherein when a first medium is introduced into some portion of the first passage and a second medium is introduced into a chamber corresponding to that respective portion of the first passage, the intracellular space of a corresponding cell in the chamber is in fluid communication with the first passage having the second medium, and at least

part of the membrane of the corresponding cell is in contact with the second medium, a corresponding sensor measures the responses of the cell to the first medium and the second medium.” As the Examiner concedes in the October 25, 2007 Office Action, Dodgson *does not teach* “that fluid moves through the first passage *to the cell*. Dodgson teaches that fluid moves through the first passage *away from the cell*.” Dodgson therefore does not teach or suggest, but instead *teaches away* from a device having the limitations of claims 7 and 18, as amended. Moreover, Rubinsky does not teach a device having these limitations and also having all the other limitations of independent claims 1 and 12, as amended. Therefore, neither Dodgson nor Rubinsky, taken alone or in combination, teach or suggest a device having all of the limitations of amended claims 7 and 18. Accordingly, individual consideration of each claim is respectfully requested.

**Claims 77 and 81:**

In the October 25, 2007 Office Action, claims 77 and 81 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson, in view of Wang. Applicant first respectfully submits that Wang is not a qualified reference because Wang claims a priority date of August 10, 2001 from the U.S. provisional application number 60/311,327, which is later than August 6, 2001, the filing date of U.S. provisional application number 60/310,652, to which the present application claims priority. Applicant understands that Wang also claims priority to another provisional application number 60/278,308, filed March 24, 2001. Applicant respectfully submits that it is the Office’s responsibility to identify whether the portions of Wang cited in the Office Action were disclosed in the provisional application number 60/278,308. Even if Wang were a qualified reference, which applicant does not agree, as set forth above, claims 77 and 81 are dependent on now allowable amended claims 1 and 12, respectively, and are therefore patentable under 35 U.S.C. §103(a) over Dodgson and Wang for at least this reason.

Claims 77 and 81 also contain additional patentable subject matter. For example, claim 77 recites a device “wherein the body portion of the second substrate further defines an intersection portion where the first passage and the first opening are in fluid communication, and wherein the intersection portion is at least partially formed as a cone shaped portion” and claim 81 recites a device “wherein the body portion of the second substrate further defines a plurality

of intersection portions where the first passage and the plurality of first openings are in fluid communication, respectively, and wherein each intersection portion is at least partially formed as a cone shaped portion.” As the Examiner concedes in the October 25, 2007 Office Action, Dodgson *does not teach* “that the intersection is partially formed as a cone shaped portion.” Moreover, Wang does not teach a device having these limitations and also having all of the other limitations of independent claims 1 and 12, as amended. Accordingly, individual consideration of each claim is respectfully requested.


### CONCLUSION

Applicant respectfully submits that the foregoing Preliminary Amendment and Response place this application in condition for allowance. If the Examiner believes that there are any issues that can be resolved by a telephone conference, or that there are any informalities that can be corrected by an Examiner’s amendment, please call the undersigned at 404.495.3678.

Respectfully submitted,

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